IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. Of:	GEORGE KRSEK		)
Serial No.:	10/823,885		)
Filed:	April 13, 2004		)
For:	PAIN RELIEF COMPOSITION . . .		)
Group:	1617		)
Examiner:	Clayton, Deidre	DOCKET: KONEC 04.02	)

Commissioner of Patents & Trademarks
Washington, D.C. 20231

DECLARATION UNDER 37 CFR 1.132

I, GEORGE R. KRSEK, Ph.D., hereby declare:

1. I am an Applicant in the above-referenced Application.

2. My invention comprises a bi-layer tablet consisting of a first layer (the "active layer") and a second layer, in combination with an encapsulant disposed over that bi-layer tablet, wherein the first layer comprises an orally therapeutically effective dose of oxycodone HCl in combination with dextromethorphan HBr.

3. My oral dosage form is prepared to include a first aperture extending through the encapsulant in combination with a second aperture which extends inwardly into the first layer.

4. When I first started work on my oxycodone/dextromethorphan dosage system, I used chloropheniramine malleate as a stalking horse for oxycodone to avoid handling a regulated narcotic drug.

5. In developing my oral dosage, I found it necessary to extend the aperture formed in the encapsulant into the active layer to achieve a desired drug release profile.

6. Later, I used selegiline hydrochloride as a stalking horse for oxycodone because that compound's solubility in water was similar to oxycodone.

7. When using selegiline hydrochloride I again found it necessary to extend the aperture formed in the encapsulant into the active layer to achieve a desired drug release profile.

8. When testing an oral dosage form comprising oxycodone and dextromethorphan I again found it necessary to extend the aperture formed in the encapsulant into the active layer to achieve a desired drug release profile.

9. Attached hereto as Exhibit "A" is a true and accurate copy of a page from my research notebook, wherein I signed and dated that page on October 24, 2003.

10. I compared the release profile of a first oral dosage form with a second oral dosage form, wherein both dosage forms comprised a bi-layer tablet comprising 210 milligrams of active ingredients in an active layer, an osmagen layer, and an encapsulant, wherein in the first oral dosage form an aperture extended through the encapsulant but did not extend into the active layer, and wherein in the second oral dosage form an aperture extended through the encapsulant and extended into the active layer.

11. Referring to Exhibit "B" hereto, the curve identified as the Ideal Release Profile shows a rapid initial release of Actives such that all 210 milligrams of Actives are released into the water within about 1 hour, and wherein no portion of the osmagen layer is released into the water.

12. I prepared a first oral dosage form comprising a bi-layer tablet consisting of an active layer comprising 175 milligrams oxycodone HCl and 35 milligrams dextromethorphan HBr (collectively the "Actives") and an osmagen layer, in combination with an encapsulant covering that bi-layer tablet.

13. I drilled a 1/16" inch diameter aperture through the encapsulant, wherein that aperture did not extend into the active layer.

14. I placed that first oral dosage form into 200 mL of water maintained at 36°C.

15. After about 1 hour, 2 hours, 3 hours, 4, hours, 6 hours, 8 hours, and 22 hours, I determined by ultraviolet spectroscopy the amount of Actives that had been released from the first oral dosage form.

16. Referring to Exhibit "B" hereto, the curve identified as the First Oral Dosage shows the measured release data for 1 hour, 2 hours, 4 hours, 6 hours and 22 hours for the first oral dosage.

17. Exhibits "A" and "B" show that after 6 hours all the Actives had not been released into water.

18. I prepared a second oral dosage form comprising a bi-layer tablet consisting of an active layer comprising 175 milligrams oxycodone HCl and 35 milligrams dextromethorphan HBr (collectively the "Actives") and an osmagen layer, in combination with an encapsulant covering that bi-layer tablet.

19. I drilled a 1/16" inch diameter aperture through the encapsulant covering the second oral dosage form, wherein that aperture did extend into the active layer.

20. In forming the second oral dosage form I advanced the drill bit about 2 mm into the active layer.

21. I placed that second oral dosage form into 200 mL water maintained at 36°C.

22. After about 1 hour, 2 hours, 4, hours, 6 hours, and 22 hours, I determined by ultraviolet spectroscopy the amount of Actives that had been released from the second oral dosage form.

23. Referring to Exhibit "B" hereto, the curve identified as the Second Oral Dosage shows the measured release data for 1 hour, 2 hours, 4 hours, 6 hours and 22 hours for the second oral dosage.

24. The release profile achieved using the second oral dosage form, wherein the aperture extends into the active layer, more closely matches the Ideal Release Profile than does the release profile measured using the first oral dosage form, wherein the aperture does not extend into the active layer.

25. In addition, Exhibits "A" and "B" show that 210 milligrams of Actives were released by the second oral dosage form into the water at or before the 4 hour measurement.

26. Exhibit "C" hereto graphically shows the cumulative amounts of Actives released over the first 4 hours from the first oral dosage form and the second oral dosage form.

27. After about 1 hour, the two oral dosage forms released about the same amount of Actives.

28. After about 2 hours, the second oral dosage form released about 1.7 times the amount of Actives as the first oral dosage form.

29. In light of the comparable amounts of Actives released by the two dosage forms after about 1 hour, the increased amount released by the second oral dosage form after about 2 hours was unexpected.

30. After about 4 hours, the second oral dosage form released about 2.6 times the amount of Actives as the first oral dosage form.

31. In light of the comparable amounts of Actives released by the two dosage forms after about 1 hour, the increased amount released by the second oral dosage form after about 4 hours was unexpected.

32. In light of the enhanced rate of release of Actives by the second oral dosage form, the reduced release of osmagen layer components by the second oral dosage layer after about 22 hours was unexpected.

33. The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

George R. Krsek

GEORGE R. KRSEK, Ph.D.

Date: 17 Sept 07

CERTIFICATE OF ELECTRONIC FILING

I hereby certify that this correspondence is herewith being electronically transmitted via Electronic Filing System to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

/Reena Mendez/	November 14, 2007
Signature	Date of Signature

EXHIBIT “A”

D (2)

Made 1 trilayer tablet as B-2
with 2.10 mg active + 190 overcoat
coated with 8 coats of dextrose 40
4 Cellulose Acetate + 1.0 PEG 4000 dry
between coats with hair dryer - blow first
30 secs. + then in oven 55° overnite -
drill 0.05" hole but not recoating the
redrill 0.10" (1/8) hole + get following
release

Start	9:00	0 in 200 ml 1% D 5W
	9:00	0.043
	10,00	0.053
	11,00	0.067 redrill
	12,00	0.087
	14:00	0.148
	16:00	0.162
next day	8:00	0.260

reground shells after 1 hr drying
+ 200 ml at 37°C - 16.19%

Made blend of 2.1 g dexpromethophan +
0.2 gm of oxycodone + 1.8 gm of avicel
Blended with N-22A + 4 gm of blend
D-2 for about 80 tabs

Made a trilayer with D-2 + N-22B overcoat
4 coats Acetate/CA/PEG - 7 coats, 1 dry coat
in 55°C oven + drill 1/8"

start	0930 - 10.45	0.055
	1205 -	0.092
	1/4 by -	0.226
	1640	0.218
Next day	10:30	0.244

Rinse 4 times

EXHIBIT “B”

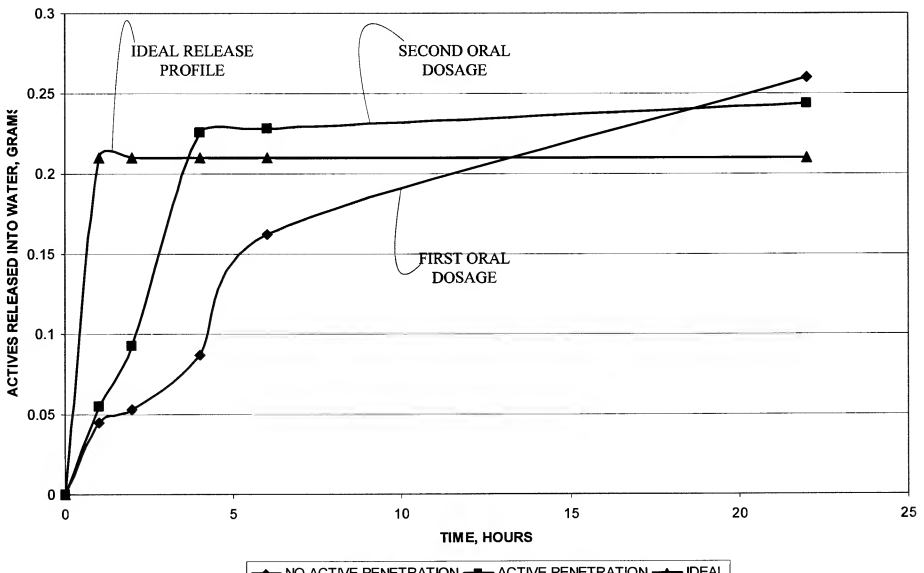
RELEASE PROFILES
IDEAL RELEASE PROFILE
SECOND ORAL DOSAGE
FIRST ORAL DOSAGE
ACTIVES RELEASED INTO WATER, GRAMS
0.3
0.25
0.2
0.15
0.1
0.05
0
0
5
10
15
20
25
TIME, HOURS
NO ACTIVE PENETRATION
ACTIVE PENETRATION
IDEAL

EXHIBIT “C”

CUMULATIVE AMOUNT OF ACTIVES RELEASED OVER TIME